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USSR INTERINSTITUTE CONFERENCE ON PROBLEMS OF
ETIOLOGY AND PATHOGENESIS OF TUMORS

Vestnik Akademii Meditsinskikh Nauk SSSR
No 1, 1954, pp 88-91
Moscow, Mar 1954

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An interinstitute conference on problems of the etiology and pathogenesis of tumors took place from 30 October to 2 December 1953 at the Institute of Experimental Pathology and Therapy of Cancer, Academy of Medical Sciences USSR. The number of participants at the conference was 479, of whom 400 were from Moscow and 79 from 26 other cities of the USSR. The three principal concepts of the cause of malignant tumors were discussed at the conference: the hypothesis of the virus etiology of tumors (A. D. Timofeyevskiy and L. A. Zil'ber), the hypothesis of the origin of cancer due to the action of cancerogenic chemical agents (L. M. Shabad), and the hypothesis in regard to the multiplicity of the causes of tumors which have a single pathogenetic origin (N. N. Petrov and L. F. Larionov).

The reports presented at the meeting resulted in a lively discussion, in the course of which many critical remarks were made. The concept of the virus origin of tumors attracted considerable attention at the meeting. During recent years the virus hypothesis has been enriched by a number of facts. L. A. Zil'ber detected specific antigens in tumor cells. A. D. Timofeyevskiy and M. A. Morozov detected elementary bodies of the virus type in the tumors of animals and human beings, while workers at the Institute of Biology and the collaborators of L. A. Zil'ber succeeded in producing antitumor immunity. A. D. Timofeyevskiy has observed the malignization of tissues in tissue cultures exposed to the action of the milk factor. In addition to this, a number of new virus tumors has been discovered. All this furnishes a basis for the contemporary virus theory of the origin of tumors.

At the same time, some discussions at the meeting show that the facts in question may be interpreted in different ways. Thus, the globular formations which have been discovered by A. D. Timofeyevskiy and M. A. Morozov are apparently viruses. It would appear that this fact alone may form the basis of the virus theory of the development of tumors. However, the interpretation of this fact varies even among the adherents of the virus theory. While M. A. Morozov and L. A. Zil'ber are of the opinion that detection of virus-like bodies in the tumor tissues of humans constitutes an adequate and definitive proof of the etiological role played by viruses in the pathogenesis of these tumors, Timofeyevskiy, on the basis of his discovery, limits himself to the conclusion that the problem of the etiological role of the globular formations he observed is subject to further investigation. As long as no data indicate that the viruses which have been detected produce the tumors in which they are contained, the assertion made by Zil'ber is premature and the experimental fact referred to cannot serve as convincing proof of the virus theory.

The results of the brilliant investigations by Timofeyevskiy on the malignization of tissue cultures, which are at present used as an argument affirming the correctness of the virus theory, may also be interpreted in different ways. Thus, it has been shown that when cultures of mouse tissue are acted upon by methylcholanthrene alone or the milk factor alone, the tissues are not subjected to malignization, while after simultaneous action on the tissue by methylcholanthrene and the milk factor, malignization sets in. On the basis of the results obtained, Timofeyevskiy and Zil'ber are of the opinion that the milk factor is the cause of tissue malignization, but recognized that L. M. Shabad had sufficient basis for his conclusion that methylcholanthrene is under the circumstances the cause of the malignization of tissues.

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Although neither conclusion has an adequate basis, it appears that the second is more justified because development of a tumor could be produced in a live mouse by the action of methylcholanthrene alone in the absence of the milk factor. The fact that the milk factor is not the cause of malignization also follows from Earl's experiments, who succeeded in producing malignancy in tissue cultures without viruses and without methylcholanthrene. It is true, however, that prolonged cultivation was necessary to achieve this effect.

The well-known data of L. A. Zil'ber, who succeeded in establishing the presence of antigen in tumor cells, attracted great attention. According to Zil'ber's assumption, the virus protein is the antigen. The fundamental significance to Zil'ber's discovery is that the qualitative difference between tumor cells and normal cells has been established experimentally for the first time. However, in their most recent investigations, Zil'ber and his collaborators found that in addition to this antigen other antigens are present in the tumor cells and that the presence of these antigens is connected with the appearance of modified globulins. In other words, Zil'ber discovered in the tumor cell a nonvirus protein which apparently determines the malignancy. However, this fact, as has been noted by V. L. Ryzhkov, may also be interpreted as against the virus theory. It is true that Zil'ber himself assumes that the appearance of cancer protein is the result of the action of tumor viruses, but this assumption has not been proved. Thus, the results of the investigation in question may be interpreted as either proving or disproving the virus theory.

It is obvious that it would not be correct to restrict the significance of the virus theory to the field of the genesis of tumors only. Immunological investigations conducted from the standpoint of immunity to infections were also reported at the meeting. In these investigations, as has been shown in the reports presented by I. N. Mayskiy and Zil'ber, very definite results were achieved. Thus, a monospecific anticancer serum has been created which reacts only with tumor cells. Furthermore, a number of vaccines have been developed with the aid of which one could immunize animals to definite tumors. The investigation by Zil'ber, in which he established that vaccination against the virus produces immunity against the virus only and does not interfere with the growth of tumors which have been induced by this virus, is very instructive. On the other hand, it has been known for a long time that immunity against a tumor is produced by vaccination with tumor cells. This indicates that a more profitable line of investigation of the problem of cancer immunity would be investigation from the standpoint of tissue immunity rather than from that of immunity to infection, as has already been noted by immunologists.

It would be appropriate to state here that the data on newly discovered virus tumors, which are used as a means of confirming the virus theory, may also be interpreted in different ways. The tumors of fish and amphibia are apparently genuine infectious diseases. As far as the Rous sarcoma is concerned, Zil'ber himself recognizes it as a nontypical malignant tumor. Only individual tumors have been definitely proven to be of virus origin. Among them, the tumor of the lactic gland of mouse strains that are highly susceptible to cancer and the Shope papilloma are unique in their genesis and are very different from human tumors.

The virological proofs of the virus origin of tumors that have been presented at the conference were not regarded as convincing by the virologist V. L. Ryzhkov. The oncological basis of the theory of the virus origin of tumors was criticized by N. N. Petrov, who stated in his report that arguments of this kind are advanced principally by biologists who are interested in viruses rather than in tumors. It was also stated at the meeting that the mass propaganda in favor of the virus theory is premature, because it creates the erroneous impression among the people that tumors are contagious (V. F. Snegirev).

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It follows from a number of critical remarks at the meeting that the virus theory cannot yet pretend to be the guiding theory for clinicists and for research workers in the field of experimental oncology. However, the virus theory should be retained as one of the possible working hypotheses.

Much attention was devoted at the conference to the chemical hypothesis of the development of tumors, according to which the sole cause of development of all tumors is chemical substances. During recent years this theory has been subjected to serious criticism and has been modified to a great extent. For instance, L. M. Shabad now refers to this theory as the biochemical rather than chemical theory. However, as has been stated in the reports given by A. D. Timofeyevskiy, A. I. Savitskiy, A. A. Solov'yev, A. V. Gorodilova, and others, all this has little changed the substance of Shabad's concept, which still remains unconvincing. Thus, Shabad still asserts that the milk factor is of endogenous origin, although virologists categorically deny the possibility of the endogenous origin of viruses, and the milk factor is undoubtedly a virus. As has been emphasized by Timofeyevskiy, Zil'ber, and Ryzhkov, Shabad still denies the significance of inflammation in the cancer, which contradicts both clinical observations and Pavlov's theory (A. A. Solov'yev). He still insists on the decisive role played by endogenous blastomogenic substances, to which he relegates hormones as well. Actually the hormone folliculin is a physiological irritant absolutely necessary for life rather than a cancerogenic substance.

At the same time, the facts which have supplied the basis for the chemical hypothesis are indisputable. There are no reasons to doubt that cancerogenic hydrocarbons have a cancerogenic effect. This fact has been proved by the successful prophylactic measures taken against various forms of industrial cancer. That these measures were successful forms by itself a sufficient basis for the retention and further development of the chemical theory as one of the working hypotheses.

The theory of the multiplicity of causes for the development of tumors has attracted great attention for what is perhaps the first time. Hitherto, this theory was regarded as a variant of Virchow's theory of irritation. Only at present has it become apparent that the theory of cancerogenic substances is an expression of Virchow's idea, while the theory of multiple causes originated at the clinic is based on fact. One must emphasize that development of the theory of multiple causes is associated with the circumstance that neither the virus theory nor the theory of cancerogenic substances may at present assume a leading position and become the guiding concept in research and clinical work. This was reflected in the reports presented by N. N. Petrov and L. F. Larionov.

The data assembled during recent years and particularly the data obtained at the oncological clinic requires the admission that precancer modifications set in prior to the development of tumors. The polyetiological nature of the precancer changes is not only well-founded, but also proved, as has been emphasized in the report by L. F. Larionov. On the basis of a number of facts and considerations, L. F. Larionov outlined the trophic theory of the development of tumors. As a basis for this theory Larionov advanced the concept of the common pathogenetic link which arises as the result of the action of many irritants. According to the theory developed by Larionov, the cause of the genesis of a tumor is the trophism that had been modified during a prolonged time both in the body in general and in the degenerated precancer tissue in particular. This theory raised a number of objections, the principal among them being that there is no adequate factual basis for the assumptions made by Larionov.

N. N. Petrov in his report cited a number of arguments against the recognition of viruses as the sole etiological factor and started from facts established recently, according to which the tumor of the lactic gland of mice can

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be produced by the action of either the milk factor, or methylcholanthrene, or estrogen in such a manner that it is apparent that only one of these factors is effective. He then arrived at the conclusion that tumor phenomena, particularly phenomena involved in the development of malignant tumors, are of a polyetiological origin. In a number of comments that have been made, the idea was expressed that an assertion to this effect may not serve as a guiding principle, that it will not be of much advantage in clinical work, and that it can not be regarded as progressive (L. A. Zil'ber, M. S. Glazunov, and others).

However, there were other comments to the effect that the concept of the multiplicity of causes of tumors, which furthermore stipulates a single pathogenesis for all tumors, is well founded and progressive. Thus, A. I. Savitskiy, who considers experimental oncologists too far removed from the clinical work on human cancer and is of the opinion that malignant tumors may be produced by a variety of cancerigenic irritants, arrived at the conclusion that one may at present regard the theory of the polyetiological genesis of cancer and of a single pathogenesis as adequately substantiated. This statement by Savitskiy was in complete accord with a comment made by N. N. Anichkov, who on opening the conference stated that the formulation of a single theory of the pathogenesis of tumors is the all-important problem of contemporary oncology, but at the same time remarked that he personally does not believe in the idea of the multiplicity of causes of tumors. Savitskiy's statement was also supported in the comments made by a number of clinicians (S. A. Kholdin, E. I. Shevchenko and others) and of experimental workers who defended the multiplicity of causes of tumors. It is characteristic that Ye. Ye. Pogossyants, whose experiments L. A. Zil'ber cited in support of the virus theory, defended the concept of the polyetiological origin of tumors.

In the concluding address which closed the meeting, Prof N. N. Blokhin, Director of the Institute of Experimental Pathology and Therapy of Cancer of the Academy of Medical Sciences USSR, stated that the discussion which was conducted made it possible to prove that there is equal justification for all of the theories on the basis of which the problem of tumors is being investigated.

However, Blokhin emphasized that independently of the theoretical concepts that pertain to the causes of the development of tumors, the cardinal problem of contemporary oncology is the cause of the appearance of cancer protein, the presence of which differentiates tumor tissue from normal tissue. This fact, which has been definitively established, must form the basis of further research on problems of the etiology and pathogenesis of tumors.

The conference passed a resolution in which it is indicated that, at present, work on the etiology and pathogenesis of tumors is being conducted along the lines corresponding to the following three theories: (1) the virus theory, (2) the theory which emphasizes the investigation of the action of chemical substances, and (3) the theory which recognizes the existence of many etiological factors, while there is a single mechanism of the development of tumors. In addition, the resolution indicated that discussion of reports given at the conference established the fact that the data presented at the conference do not furnish an adequate basis for ascribing a leading role in the etiology of tumors to any single factor of either a virus nature or a chemical nature. However, the resolution regards as expedient further verification of the question of the virus etiology of human tumors combined with a study of the role of hormones in the pathogenesis of these tumors. The resolution emphasized that these investigations must be conducted on the basis of Pavlov's physiological teachings.

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One should note that a sufficient amount of data on the pathogenesis of tumors was not presented at the conference, while pertinent data presented by L. F. Larionov were not discussed adequately. Insufficient data were also presented on the role of the nervous system in the process of development of cancer. The data outlined by A. A. Solov'yev, R. Ye. Kavetskiy, and Olenov have not received an adequate evaluation. This was apparently due to the fact that the attention of the people who had organized the conference was concentrated on problems of the etiology of tumors. As a result many institutes at which work on tumors is being conducted have not been invited to participate actively at the conference. However, on the whole, the conference that has been held will prove to be of great significance because it will induce many investigators to subject their theoretical concepts to serious reflection and perhaps revise these concepts as a result.

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